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By: _____
Lois M. Simón

PATENT
Docket No.: 015662-000900US



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Micheline Markey, John W. Shell, Bret Berner

Application No.: 09/432,881

Filed: November 2, 1999

For: PHARMACOLOGICAL INDUCEMENT OF THE FED MODE FOR ENHANCED DRUG ADMINISTRATION TO THE STOMACH

Examiner: Edward Webman

Art Unit: 1617

COMMUNICATION

Commissioner for Patents
P.O. Box 1450
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Sir:

In response to the Office Action dated March 17, 2003, Applicants request reconsideration and reexamination on the basis of the comments herein.

Claims 1, 2, 6, 14-18, and 48-51 stand rejected under 35 U.S.C. 103 over the combination of Shell, Acharya, Sewester et al. and Hsiao. Applicants submit that the proposed combination is not one that would be made by those skilled in the art, and does not render the claimed invention obvious.

The claims under examination are to a composition that contains a fed mode inducing agent, in an amount that induces the fed mode, combined with a solid matrix that releases a drug when the matrix is in the stomach, and that is large enough when in the stomach to promote gastric retention during the fed mode.

Shell, as stated by the examiner, teaches a controlled release composition that comprises an active drug and a solid matrix that swells or expands upon contact with gastric fluid in the fed mode.

Acharya et al. contains disclosures relating to controlled release formulations of active ingredients in general, and to a specific type of such formulation in particular. However, the effective disclosure of Acharya et al. relates to controlled release formulations that are designed for use in connection with mucous membranes of the body.

The most specific type of dosage form that is disclosed and is highly emphasized by Acharya et al. is one that is specifically formulated and configured for drug delivery in the mouth. The component in the Acharya et al. dosage form that controls the situs and manner of drug release is calcium polycarbophil, which is a bioadhesive typically used in vaginal products because of its tendency to adhere to the vaginal wall and other mucous membranes.

In Acharya et al. the mucous membrane involved is the inside of the mouth. The dosage form is placed in the mouth for oral, gingival, or buccal delivery of the drug. The localized delivery is the result of the adherence of the polycarbophil to the oral, gingival, or buccal areas for an extended period of time (see column 3, lines 38-42). Note the statement in Acharya at column 7, lines 14-17: "Most preferably, the shape of the polycarbophil follows the natural contour of the mouth ...," and at lines 31-33, in the statement: "While so present the hydrated polycarbophil acts to humidify the mouth, while in some instances also stimulating saliva production." All of these effects are achieved as a result of the retention of the dosage form in the mouth. Thus, the drugs that are disclosed in Acharya et al. are not "retained in a solid matrix in a manner causing release of said drug from said solid matrix when said solid matrix is in the stomach ...",

as required by the present claims. Instead, they are retained in a solid matrix in a manner causing release of the drugs in the mouth, or alternatively, another mucous membrane – but not the stomach. This is a difference in the matrix itself, specifically in its composition.

Combining the Acharya et al. disclosure with that of Shell amounts to considering a dosage form that is specifically designed to remain in the stomach together with one specifically designed to remain in the mouth. The two references disclose controlled release formulations for different applications. Each type of formulation has specific characteristics that make it suitable for use in those applications. It is neither logical nor likely that one skilled in the art would take ingredients from one formulation and transfer them to the other with the expectation that their usefulness or the function served by their presence in the mouth or another mucous membrane would be the same in the stomach. Accordingly, the combination of Shell and Acharya et al. does not lead one skilled in the art to include docusate, or any of the drugs disclosed by Acharya et al. in a gastric-retentive dosage form such as that disclosed by Shell.

As previously noted, the Sewester et al. disclosure describes docusate as a fecal softener, a function that is served in the colon. Acharya et al. likewise state that docusate is to be used as a laxative. For effective use in a controlled release formulation, a laxative should be formulated so as to be released in the colon. However, release of sodium docusate [or another fed mode inducer] into the colon would not produce the desired fed mode inducing effect in the claimed compositions.

The examiner cites Hsiao as teaching release of docusate in the stomach. This is correct. However, the compositions of Hsiao are designed to release docusate for its usual use, i.e., as a laxative, so that even though released in the stomach the Hsiao formulation is designed so that the docusate passes from the stomach into the intestine and then the colon, to serve its normal purpose. Hsiao does not disclose any formulation such as Applicants', which is designed to induce the fed mode, resulting in retention of the docusate in the stomach.

Finally, the examiner cites the known use of docusate as a laxative, as in Acharya, as a basis for adding docusate to the Shell compositions to achieve the additional beneficial effect of providing a laxative. However, combination of drugs with laxatives in general, and with docusate in particular, is contrary to normal pharmaceutical practice.

In general, laxatives are not used in combination with other drugs, as laxatives are known to produce adverse effects either on the performance of the drug or to the patient. Applicants submit herewith (in the accompanying Supplemental Information Disclosure Statement) two standard references documenting this point.

In "AHFS Drugs 2000" in the Section "Drug Interactions", these statements are made (p. 2624):

> " By increasing intestinal motility, all laxatives may potentially decrease transit time of concomitantly administered drugs and thereby decrease their absorption.
>
> ....
>
> Stool softeners (i.e. docusate salts) theoretically may enhance the absorption of many orally administered drugs.
>
> ...
>
> Oral stool softeners should not be administered concurrently with oral mineral oil, and some clinicians recommend that stool softeners not be administered concurrently with any oral drug having low therapeutic indices."

In "Goodman & Gilman's The Pharmacological Basis of Therapeutics" (Ninth Ed., 1996), the following statement concerning combination effects of docusates is made:

> "Docusates increase the intestinal absorption and toxicity of other drugs administered concurrently, such as phenolphthalein, mineral oil and quinidine."

Thus, inclusion of a laxative such as docusate in a formulation with another drug is contrary to established general practice and would not be done by those skilled in the art.

The only common ground between Acharya and Shell is that their formulations are designed for controlled release. Aside from that, the disclosures are irrelevant to each other since each is focused on a distinct and different portion of the gastrointestinal tract, and the results achieved are specifically intended to occur only in those portions of the tract. In addition, one would not normally combine a laxative such as the docusate disclosed in Acharya or Hsiao with another drug such as those in Shell.

For completeness, Applicants wish to point out that, in addition to its use as a laxative, sodium docusate is also known for use as a surfactant or wetting agent in pharmaceutical compositions. Indeed, such use is disclosed in two references cited in the corresponding PCT Search Report, U.S. patent 4,871,546 (Feltz et al.) and British patent 1,330,829 (Smith Kline & French). However, when used for this purpose, the amount of docusate is far less than that used either as a laxative or as a fed mode inducer. In Feltz et al. the amount of docusate is 0.05-0.10 mg per tablet; in Smith Kline it is 0.0129 g. As disclosed in the specification hereof, the effective amount of docusate as a fed mode inducer is from about 30 to about 1000, most preferably from about 50 to about 400, mg. In Goodman & Gilman the effective amount of docusate as a laxative is given as 50-500 mg daily. Thus, while docusate is known to be used as a surfactant in a composition containing drugs, it is used only in a significantly smaller amount than when used as a laxative.

## CONCLUSION

In view of the foregoing, Applicants submit that the claims under examination are allowable, and request that examination proceed to the remainder of the non-elected species of claim 1, in accordance with the procedure set forth in MPEP section 803.02.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned.

Respectfully submitted,

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